MAYO CLINIC LABORATORIES

Test Definition: FET

Iron, Liver Tissue

Overview

Useful For
Diagnosis of hemochromatosis using liver tissue specimens

Testing Algorithm
For more information see Hereditary Hemochromatosis Algorithm.

Special Instructions
- Hereditary Hemochromatosis Algorithm

Method Name
Inductively Coupled Plasma Mass Spectrometry (ICP-MS)

NY State Available
Yes

Specimen

Specimen Type
Liver Tissue

Necessary Information
Patient's date of birth is required to calculate iron index.

Specimen Required
Supplies: Metal Free Specimen Vial (T173)
Container/Tube:
Preferred: Mayo metal-free specimen vial
Acceptable: Paraffin block, with no more than 1 or 2 cuts previously made
Specimen Volume: 2 mg
Collection Instructions: Two mg of liver tissue are required. This is typically a piece of tissue from a 22-gauge needle biopsy at least 2 cm long. If an 18-gauge needle is used, the tissue must be at least 1 cm in length.
Specimen Stability Information:
Fresh or formalin-fixed liver tissue specimens: Frozen (-30 to -10 degrees C) at least 20 years
Paraffin-embedded (block) liver tissue specimens: Ambient (16 to 24 degrees C) at least 12 1/2 years
Additional Information: Paraffin blocks will be returned 7 days after analysis is complete.

Specimen Minimum Volume
Needle biopsy: See Specimen Required; 2 mm x 2 mm (punch): 0.3 mg by dry weight

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Liver Tissue	Refrigerated (preferred)		
	Ambient		
	Frozen		

Clinical & Interpretive

Clinical Information

Hemosiderosis is the condition of excessive iron accumulation in tissues. Liver is the first organ affected in iron-overload diseases. Transient increases in iron first appear in Kupffer cells. This finding is commonly related to sideroblastic anemia, excessive iron consumption, or chronic alcohol ingestion. Persistent hemosiderosis, as seen in hemochromatosis, causes iron accumulation in hepatocytes and is usually concentrated in biliary cells.

Hereditary hemochromatosis is an autosomal recessive disease with estimated prevalence of 2 in 1000 in White population, with lower incidence in other races. The gene responsible for hereditary hemochromatosis (*HFE*) is located on chromosome 6; the majority of patients with hereditary hemochromatosis have variants in the *HFE* gene. Hereditary hemochromatosis is characterized by an accelerated rate of intestinal iron absorption and progressive iron deposition in various tissues that typically begins to be expressed in the third to fifth decades of life but may occur in children. The most common presentation is hepatic cirrhosis in combination with hypopituitarism, cardiomyopathy, diabetes, arthritis, or hyperpigmentation. Because of the severe sequelae of this disease, if left untreated and recognizing that treatment is relatively simple, early diagnosis before signs or symptoms appear is important.

Screening for hemochromatosis is best done by measuring serum iron and transferrin saturation (FEC / Iron and Total Iron-Binding Capacity, Serum). If the serum iron concentration is above 175 mcg/dL and the transferrin saturation is above 55%, analysis of serum ferritin concentration (FERR1 / Ferritin, Serum) is indicated. A ferritin concentration above 400 ng/mL is suggestive of hemochromatosis but also can indicate other forms of hepatocyte injury, such as alcoholic or viral hepatitis, or other inflammatory disorders involving the liver. *HFE* analysis (HFET / Hereditary Hemochromatosis, *HFE* Variant Analysis, Varies) may be used to confirm the clinical diagnosis of hemochromatosis, to diagnose hemochromatosis in asymptomatic individuals with blood tests showing increased iron stores, or for predictive testing of individuals who have a family history of hemochromatosis. The alleles evaluated by *HFE* gene analysis are evident in approximately 80% of patients with hemochromatosis; a negative report for *HFE* gene does not rule-out hemochromatosis. In a patient with negative *HFE* gene testing, elevated iron status for no other obvious reason, and family history of liver disease, additional evaluation of liver iron concentration is indicated.

Diagnosis of hemochromatosis may also be based on biochemical analysis and histologic examination of a liver biopsy. In this assay, results are reported as the hepatic iron index (HII) and dry weight of iron. The HII is considered the "gold standard" for diagnosis of hemochromatosis. This test is appropriate when:
-Serum iron is above 160 mcg/dL

-Transferrin saturation is above 55%
-Ferritin is above 400 ng/mL in male patients or above 200 ng/mL in female patients
-*HFE* gene test is negative for *HFE* variants

For more information see Hereditary Hemochromatosis Algorithm.

Reference Values

Iron
Males: 200-2,400 mcg/g dry weight
Females: 200-1,800 mcg/g dry weight

Iron Index
> or =13 years: <1.0 mcmol/g/year
Reference values have not been established for patients that are younger than 13 years.

Interpretation

A hepatic iron concentration above 10,000 mcg/g dry weight is diagnostic for hemochromatosis.

Hepatic iron concentrations above 3000 mcg/g are seen when there is iron overload without cellular injury and cirrhosis. Hepatic iron concentrations greater than the reference range are associated with hemosiderosis, thalassemia, and sideroblastic anemia. Some patients with hepatitis or cirrhosis without significant fibrosis will have hepatic iron concentrations at the top end of normal or just slightly above the normal range.

Iron accumulates in the liver normally with aging. The hepatic iron index (HII) normalizes hepatic iron concentration for age. The HII is calculated from the hepatic iron concentration by converting the concentration from mcg/g to mcmol/g dry weight and dividing by years of age. The normal range for HII is less than 1.0.
-Patients with homozygous hemochromatosis have an HII above 1.9.
-Patients with heterozygous hemochromatosis often have an HII ranging from 1.0 to 1.9.
-Patients with hepatitis and alcoholic cirrhosis usually have an HII below 1.0, although a small percentage of patients with alcoholic cirrhosis have an HII in the range of 1.0 to 1.9.
-Patients with hemochromatosis who have been successfully treated with phlebotomy will have an HII below 1.0.

Liver specimens collected from patients with cirrhosis containing a high degree of fibrosis have results near the low end of the reference range, even though they will show significant iron staining in hepatocytes. While it is true that iron accumulates in hepatocytes in advanced alcoholic cirrhosis with fibrosis, there are relatively few hepatocytes compared to other inert (fibrotic) tissue, so the quantitative iron determination, which is expressed as microgram of iron per gram of dry weight tissues, yields a low result. Histologic examination of all tissue specimens should be performed to facilitate correct interpretation. When structural heterogeneity is apparent histologically, variation in measured iron should be anticipated. In approximately 2% of cases, a high degree of hepatic heterogeneity has been observed that makes quantitation highly variable.

Cautions

Formalin-fixed, paraffin-embedded tissue can be used when histologic examination (including iron stains) is requested in addition to the hepatic iron concentration and calculated hepatic iron index; however, fresh or frozen tissue is preferred.

Paraffin blocks from which many slides have been previously cut often appear to contain sufficient quantity of tissue,

however, the specimen is often very thin and less than 2 mg in weight.

Clinical Reference

1. Brandhagen DJ, Fairbanks VF, Baldus W. Recognition and management of hereditary hemochromatosis. Am Fam Physician. 2002;65:853-860, 865-866
2. Summers KM, Halliday JW, Powell LW. Identification of homozygous hemochromatosis subjects by measurement of hepatic iron index. Hepatology. 1990;12:20-25
3. Ludwig J, Batts KP, Moyer TP, et al. Liver biopsy diagnosis of homozygous hemochromatosis: a diagnostic algorithm. Mayo Clin Proc. 1993;68:263-267
4. Pietrangelo A. Hemochromatosis: an endocrine liver disease. Hepatology. 2007;46:1291-1301
5. Ashley EA, Butte AJ, Wheeler MT, et al. Clinical assessment incorporating a personal genome. Lancet. 2010;375:1525-1535
6. McLaren CE, Barton JC, Eckfeldt JH, et al. Heritability of serum iron measures in the hemochromatosis and iron overload screening (HEIRS) family study. Am J Hematol. 2010;85:101-105
7. Radford-Smith DE, Powell EE, Powell LW. Haemochromatosis: a clinical update for the practising physician. Intern Med J. 2018;48(5):509-516. doi:10.1111/imj.13784

Performance

Method Description

The metal of interest is analyzed by inductively coupled plasma mass spectrometry.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Monday, Thursday

Report Available

3 to 6 days

Specimen Retention Time

60 days

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Superior Drive

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.

- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

83540

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
FET	Iron, Liver Ts	57028-3

Result ID	Test Result Name	Result LOINC® Value
8350	Iron, Liver Ts	57028-3
7770	Hepatic Iron Index	49061-5